

MenAfriVac: an example of efficient technology transfer to develop a needed vaccine

Suresh Jadhav, Serum Institute of India, LTD and
Jean-Marie Preaud, PATH

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*Eliminating epidemic
meningitis as a public health
problem in sub-Saharan Africa*

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Epidemic meningitis in Africa

Meningitis belt: extends from Ethiopia to Senegal: Sudan, Ethiopia, Chad, Niger, Northern Nigeria, Burkina Faso, Mali are considered hyper-endemic

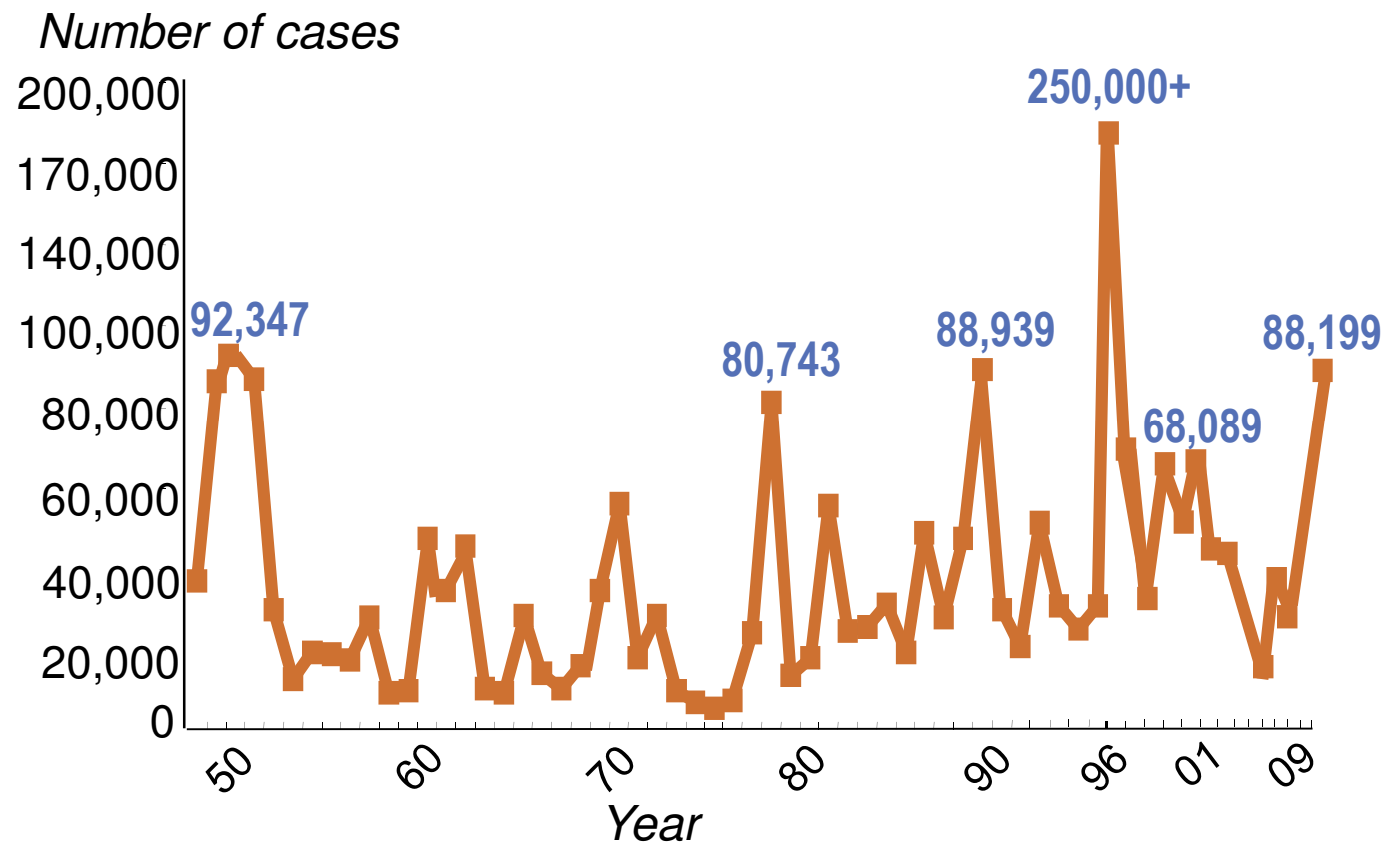
1905: first documented epidemic, Northern Nigeria

1919-1924: second cycle with over 45,000 deaths in Northern Nigeria

1935-1937: third cycle: Nigeria 6456 deaths

1951-60: 340,000 cases with 53,000 deaths

1996-1997: 300,000 cases with 30,000 deaths



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The Meningitis Vaccine Project: an example of “push” funding to develop a new vaccine

- Created in June 2001 by a grant from the Bill & Melinda Gates Foundation as a 10 year partnership between WHO and PATH
- Goal: to eliminate epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, licensure, and widespread use of *conjugate* meningococcal vaccines
- **Guiding Principles**
 - The project is about public health impact and not simply making vaccines available
 - Decisions about candidate vaccines linked to introduction strategies and likely financial constraints



African public health officials to be closely involved with MV

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Development of MVP - History

- Renewed interest in conjugate vaccines at WHO after the 1996-1997 epidemic
- EVA (Epidemic Vaccines for Africa) project established at WHO (Dr. Luis Jodar)
- In-depth discussions with vaccine manufacturers in 1999 and 2000; costing model for conjugate vaccines developed; evolution of a collaboration between WHO and CVP/PATH



Choice of Men A Conjugate Vaccine

- After extensive discussions with WHO, advisory groups and African public health officials a decision was made to develop a monovalent meningococcal A vaccine because:
 - Continued Men A epidemics in the 1990s
 - Field tests in Niger and The Gambia with conjugate vaccines developed by Pharma
 - Development stopped in late 1990s
 - Products not deemed commercially viable
 - Opportunity costs too high
 - No Men A conjugate vaccine available as of 2001
 - Advantage of simplicity, less risk and solid public health impact



Discussions with African Public Health Officials & WHO/AFRO, Fall 01-Spring 02

- Cost of vaccine was the most important limiting factor to the introduction of new vaccines
- Meningitis belt countries are the poorest in the world
- Success of MVP (widespread use of a conjugate meningococcal vaccine in mass campaigns) would not be possible unless vaccines were priced less than \$US 0.50 per dose



MenA conjugate vaccine development

- Could not reach agreement with major vaccine manufacturers; negotiations ended in March 02
- MVP decided to pursue development of a Men A conjugate vaccine using a different strategy:
- Creation of a consortium to do the following:
 - Identify sources of raw materials (Men A PS and tetanus toxoid)
 - Identify a conjugation method
 - Find a vaccine manufacturer willing to accept technology transfer (fermentation and conjugation) and make the conjugate vaccine at a price less than \$US 0.50 per dose



Men A Conjugate Vaccine Development

- By mid 2002 MVP began working with Serum Institute of India as a key member of a consortium that was created and managed by MVP to develop a new and affordable Men A conjugate vaccine.
- Over the next two years the consortium
 - identified raw materials (Men A PS and tetanus toxoid)
 - licensed a conjugation method
 - transferred fermentation/purification and conjugation technology to SIIL



Licensure, Prequalification, and Introduction of MenAfriVac™

- MenAfriVac™ licensed by Drugs Controller General of India in December 2009
- WHO prequalified in June 2010
- First introduction in Burkina Faso, Mali, and Niger in September to December 2010



Management of intellectual property

- Licensing agreement for the intellectual property developed with NIH (acting on behalf of FDA)
- Territory defined as countries with lower to upper middle income economies as defined by the WB
- Patent costs borne by MVP



Access of Men A conjugate vaccine to meningitis belt countries

Vaccine	Year available in USA	Year first introduced in dev. country	Lag period: time from USA to introduction in develop. country (yrs)	Scale up: Number of years to 25 million doses used in develop. countries	Lag period for scale up: years from develop. country intro to 25 million doses
HebB	1982	1994	12	2001	7 yrs
HiB	1990	2001	11	2008	7 yrs
MenA	2005 A/C/Y/W*	2010 A	N/A	2010 (proposed)	0

*age indication not appropriate for Africa



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Characteristics of MenA vaccine development

- North/South transfer of technology not currently available
- South/South transfer of a vaccine product at an affordable price
- Capacity building for Indian and African clinical investigators
- Model for other vaccines/products





**World
Health
Organization**



SERUM INSTITUTE OF INDIA LTD.



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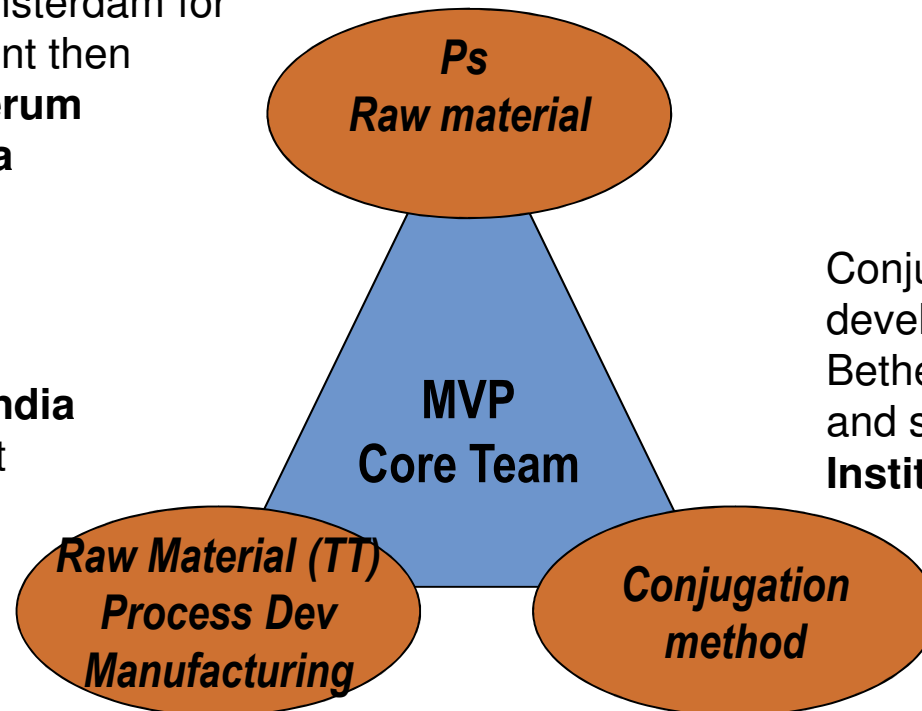
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The MVP Men A vaccine development model

A PS produced by **SynCo BioPartners**, Amsterdam for initial development then transferred to **Serum Institute of India**

Serum Institute of India
process development
and manufacturing

Lyophilization and
stabilization tech
transfer from
Aerial in France to
Serum Institute



Conjugation method
developed at **CBER/FDA**,
Bethesda, USA, transferred
and scaled-up at **Serum
Institute of India**

Target price US\$ <0.50/dose



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Product development

- **SynCo BioPartners** in Amsterdam agreed to provide the Men A Polysaccharide for the project
- Conjugation method developed at **CBER/FDA**, Bethesda, USA and transferred to **Serum Institute of India, Ltd**
- **Serum Institute of India Ltd** to furnish tetanus toxoid and manufacture vaccine
- Formulation and lyophilization of the MenA conjugate vaccine developed at **Aérial**, Illkirch, France and transferred to **SIIL**.



Technology transfer from Synco Biopartners to Serum Institute of India Limited:

Production of purified MenA polysaccharide



Technology transfer from Synco to SIIL (1):

Fermentation and purification of Men A

■ Purpose

- 18 October 2004 – 12 November at Synco BioPartners, Amsterdam
- Training of three SIIL scientists: Mr S. Purandare, Mr J. Joshi, and Dr S. Beri
- Trainer: Mr P. Dissel

■ Scope

- Training was done by running two fermentation batches, each of 7 liter-scale followed by two purification batches at pilot scale
- Discussions on documentation: process flow chart, in-process controls, batch protocol records
- Daily wrap-up meetings to answer questions from trainees. Minutes are recorded
- SOPs, raw materials specifications, and equipment references for the production process at pilot scale were furnished
- Final wrap-up meeting on November 12th to conclude the success of the technology transfer. Participants: SIIL (Dr Kapre, Dr S. Beri, Mr J. Joshi), SynCo (Mr Paul Dissel, Mr Edwin van den Bos), and PATH (Dr M. LaForce, Mr. JM Préaud)



Technology transfer from Synco to SIIL(2):

Preparation of cell banks

- Reception of M1027 strain from Dr Carl Frasch (CBER)
- Preparation of Men A non-GMP working cell bank for development purpose
- Preparation of GMP master cell bank (MCB) and working cell bank (WCB) for production of clinical material
 - Synco with Cobra carried out the preparation of the GMP MenA MCB and WCB
 - Synco carried out the stability studies of the MenA MCB and WCB till 24 months. Then, SIIL continued stability studies.
 - Synco organized the shipment of MCB and WCB from Amsterdam to SIIL



Technology transfer from Synco to SII(3): *Preparation of master cell bank and working cell bank*



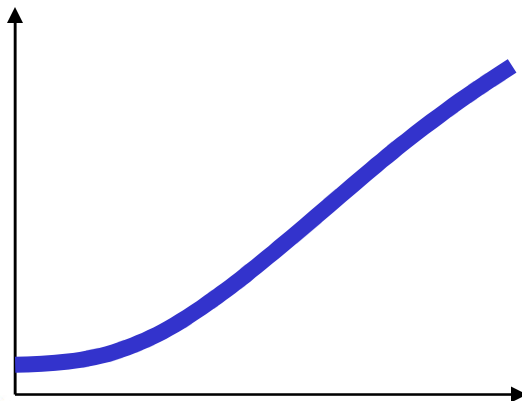
- Operations under Good Manufacturing Practice (GMP)
 - First step of fermentation in glass flasks (erlen meyer)
 - at controlled room temperature
 - Lyophilization in ampoules (100 million bacteria per 1-ml ampoule)
 - Testing: characterization, purity, titer, stability
 - Storage at – 70° C



Technology transfer from Synco to SIIL(4): *Fermentation of MenA polysaccharide*



- **Determination of critical parameters: pH, temperature, agitation, media volume...**
- **In process controls: viability, purity**
- **Design of equipment**
- **Documentation (batch protocol records):**
 - AP-BPR-MEA-2850: Preparation of Men Inoculum for MEA production
 - AP-BPR-MEA-2900: Production of Men A at 5L scale, Fermentation



Technology transfer from Synco to SIIL (5):

Extraction and purification of MenA polysaccharide



- Determination of critical parameters
- Design of equipment
- In process controls
- Documentation (batch protocol records):
 - AP-BPR-MEA-2950: Production of Men A at 10L scale, Primary recovery
 - AP-BPR-MEA-3000: Extraction of Men A polysaccharide out of CTAB wet paste
 - AP-BPR-MEA-3005: Concentration and precipitation of Men A polysaccharide
 - AP-BPR-MEA-3010: Dissolving, diafiltration precipitation and drying of polysaccharide



Technology transfer from Synco to SIIIL (6):

Summary

- Technology transfer of preparation of MCB, WCB, fermentation and purification have been successful at pilot scale
- Consequently, scale up of technologies has been performed at industrial scale at SIIIL
- Biocomparability protocols have shown that the material produced by SIIIL is qualitatively comparable to the material produced by Synco
- Consistency lots have been prepared and used for clinical trials



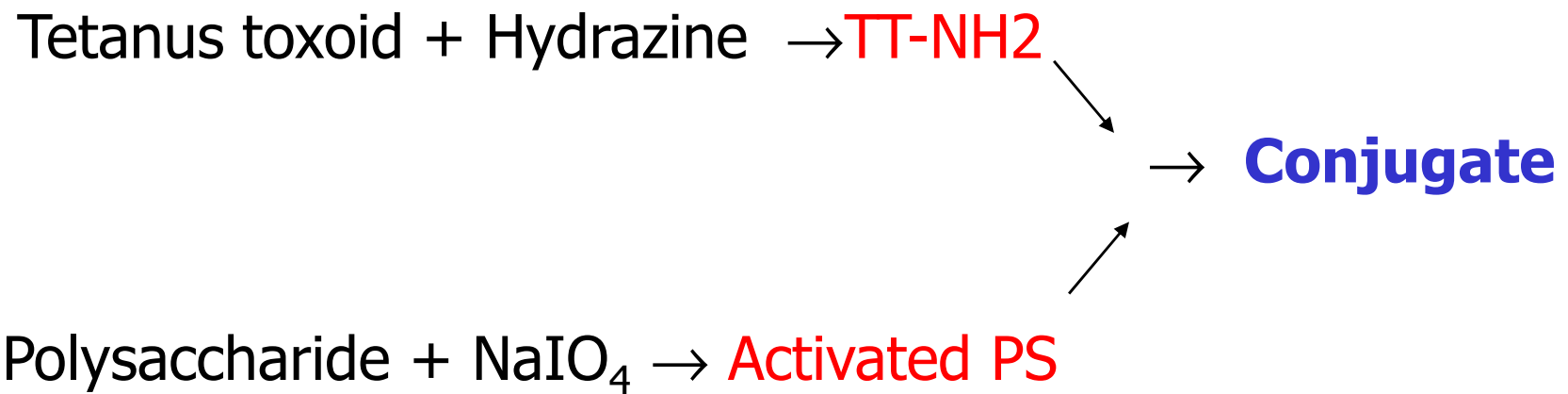
Technology transfer from CBER to Serum Institute of India Limited:

Preparation of MenA polysaccharide - tetanus toxoid conjugate



Technology transfer from CBER to SIIL (1):

Preparation of PsA-TT conjugate - The Lee/Frasch method



Technology transfer from CBER to SIIL (2) :

Conjugation method

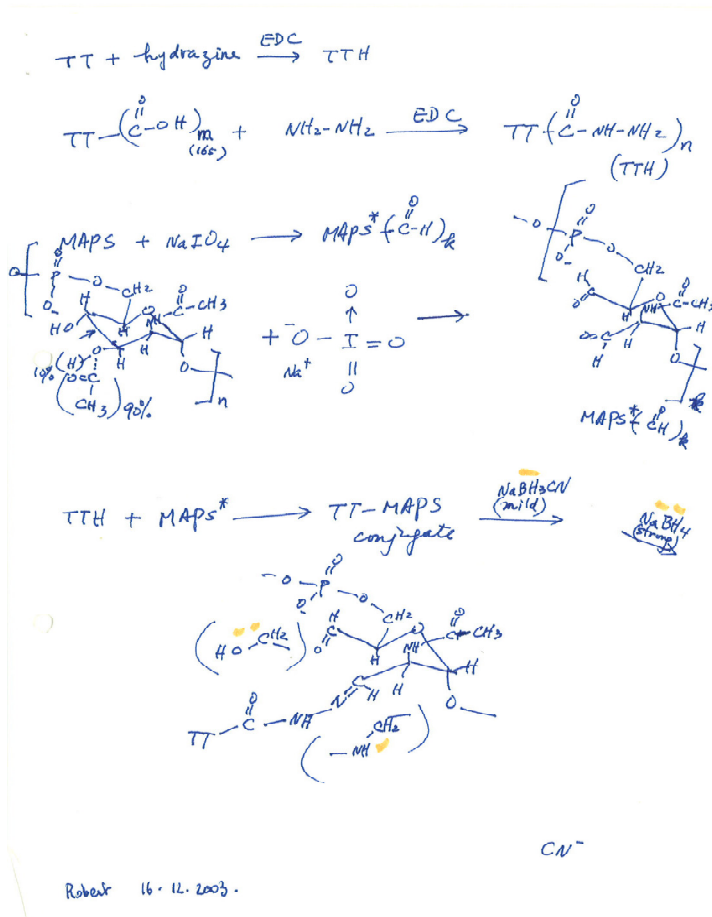


- December 2003 - CBER
- Under the supervision of Dr Carl Frasch and Dr Robert Lee
- Two SIIL scientists worked at CBER for three weeks
 - Learning conjugation method
 - Duplicating process at lab scale
 - Receiving SOPs for conjugation process and analytic methods



Technology transfer from CBER to SIIL (3)

Conjugation method



- December 16th, 2003, at **CBER:**

- first conjugation lesson**

- Objective

Transfer the conjugation technology (production process and analytical methods) from CBER to SIIL

- Methodology

- Presentation of SOPs
- Demonstration by R. Lee
- Hands on by Indian team
- Daily follow up: Q&A with C. Frasch & R. Lee



Technology transfer from CBER to SIIL (4)

List of Standard Operational Procedures provided to SIIL

■ **Production process**

- SOP00001: Activation of tetanus toxoid
- SOP00002: Activation of meningococcal group A polysaccharide
- SOP00003: Conjugation of activated Men A PS to activated TT

■ **Analytical methods**

• **Characterization of activated tetanus toxoid**

- SOP00004: Lowry assay for quantification of protein
- SOP00006: TNBS assay for hydrazine content
Determination of degree of activation for TTH

• **Characterization of activated Men A PS**

- SOP00007: Modified resorcinol assay for quantification of Men A PS
- SOP00008: Phosphorus assay for quantification of Men A PS
- SOP00009: Determination of degree of activation for Men A PS
- SOP00010: Preparation of activated/reduced Men A PS (for analysis)

• **Characterization of TT-MAPS conjugate product**

- SOP00004: Lowry assay for quantification of protein
- SOP00005: Protein quantification by measurement of absorbance at 280 nm
- SOP00007: Modified resorcinol assay for quantification of MAPS
- SOP00008: Phosphorus assay for quantification of MAPS
Determination of ratio [protein]/[MAPS]



Technology transfer from CBER to SIIL (5)

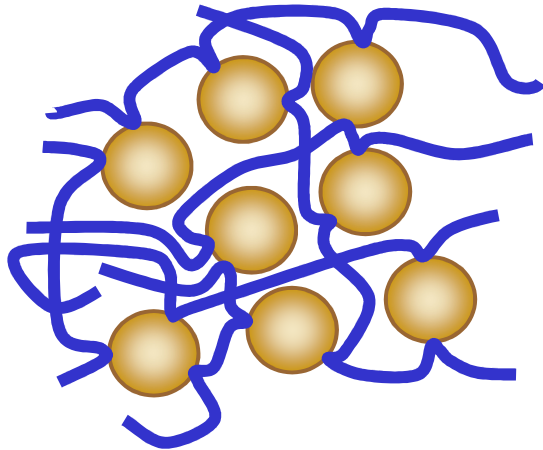
Conclusions

- Technology transfer
 - Production process and analytical methods transferred to SIIL team after a three-week intensive training at CBER (Bethesda), including the preparation of six lab-scale batches (10mg and 25mg of PsA)
 - The technology of conjugation is well controlled by Indian scientists
- Next step: Implementation of the method at SIIL (Pune)



Technology transfer from CBER to SIIL (6)

The Lee/Frasch conjugation method



Structure of CBER/SIIL Men A Conjugate Vaccine



- **January to March 2004: at SIIL – Pune**
 - Implementation of the Lee/Frasch method
 - Scale up to pilot scale (100 mg)
 - Technical support from CBER scientists who visited SIIL (February 2004)
 - Three lots of Men A conjugate sent from SIIL to NIBSC for testing (March 20, 2004)
 - Murine immunologic studies done at NIBSC and SIIL
 - Data presented at Expert Panel Meeting in June 2004
- Strong scientific support from experts: Dr C. Ceccarini, Dr J. Petre, Dr N. Ravenscroft



Technology transfer from CBER to SIIL (7)

Summary

- Technology transfer of Lee/Frasch conjugation method has been transferred successfully to SIIL at lab scale (10 to 25 mg)
- Subsequently, the method has been developed at pilot scale (100 mg). The material produced has been tested and released for the Phase I clinical trials
- Then, the method has been developed at industrial scale (100 g)
- Biocomparability protocols have shown that the materials produced at lab scale, pilot scale, and industrial scale are qualitatively comparable
- Subsequently, the lots produced at industrial scale have been tested and used for the Phase II and Phase III clinical trials



Collaboration with A  rial:

Formulation and lyophilization development of MenAfriVac



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Collaboration with Aériel

Formulation and lyophilization development of MenAfriVac

1. Contract with Aériel, Illkirch, France
2. Supported by PATH
3. All objectives achieved
 - Vaccine stable: Free polysaccharide not more than 30% over 2 years at 2-8 degrees Celsius
 - % moisture not more than 2%
 - Acceptable cake appearance
 - Lyophilization cycle reduced, therefore increasing the lyophilization capacities of production at SIII
 - Reconstitution time not to exceed 10 seconds
 - The conjugate material is intact based on HPLC profiles



Why the tech transfers went well

- All parties committed to the goal of the project
- All activities covered contractually
- Mutual respect among all parties
- Communication, communication and more communication...through periodic conference calls, annual review meetings
- Excellent technical staff
- Excellent document management
- Rapid decision-making process
- Strong support from the top and from the bottom



Technology transfers to Serum Institute



- Technology transfers and scientific cooperation were successful because of:
 - The support of expert consultants
 - Agreed goals shared by all partners
 - Mutual respect
 - Communication, communication and more communication...



Men A conjugate vaccine - “MenAfriVac”



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Thank you

The Meningitis Vaccine Project



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